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APPLICATION NO.	FILING DATE	PERSON NAMED INVENTOR	ATTORNEY (Firm Name)	COMMUNICATION NO.
08 950,542	10/15/1997	WILLIAM W. BACHOVCHIN	2002041-0081	9498

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EXAMINER

LUKTON, DAVID

ARTICLE PAPER NUMBER

DATE MAILED 12/31/2002

89

Please find below and or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

08/950,542

Applicant(s)

Bachovchin

Examiner

David Lukton

Art Unit

1653



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Oct 10, 2002
- 2a) This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 35, 36, 39-43, and 46-51 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 35, 36, 39-43, and 46-51 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are a) _____ accepted or b) _____ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) _____ approved b) _____ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some* c) None of:
- Certified copies of the priority documents have been received.
 - Certified copies of the priority documents have been received in Application No. _____.
 - Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- *See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

2 Notice of Draftsperson's Patent Drawing Review (PTO 944)

5 Notice of Informal Patent Application (PTO 152)

3 ☒ Information Disclosure Statement (PTO 1449, Paper No. s

58

6 Other

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/10/02 has been entered.

Pursuant to the directives of paper No. 52 (filed 5/6/02), claims 35 and 42 have been amended, and claims 37, 38, 44, 45 cancelled. Claims 35, 36, 39-43, 46-51 are pending. Applicants' arguments filed 10/10/02 have been considered and found not persuasive.

✱

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35, 36, 39-43, 46-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As indicated previously, the specification does not enable a skilled organic chemist to

two species that fall within the scope of the claimed invention: Pro-boroPro and Ala-boroPro. As disclosed on page 15, line 3+ of the specification, L-Ala-D-boroPro can be separated from L-Ala-L-boroPro by eluting with MeOH/EtOH on silica gel. On page 21, line 13+, it is stated that L-Pro-L-boroPro can be separated from L-Pro-D-boroPro by eluting the compounds on a C₁₈ HPLC column using a water/acetonitrile gradient. As stated in the declaration filed 4/6/99 (paper No. 29), the conclusion that L-Ala-D-boroPro can be separated from L-Ala-L-boroPro by eluting with MeOH/EtOH on silica gel is erroneous. The reason for this erroneous conclusion is the presence of the following four different isomers, a fact which was not recognized at the time:

cis-L-Ala-D-boroPro and *trans*-L-Ala-D-boroPro

cis-L-Ala-L-boroPro and *trans*-L-Ala-L-boroPro.

According to the declaration, the spectra were misinterpreted, and the stereochemistry incorrectly assigned. This admission of misinterpretation supports a finding of non-enablement, at least insofar as the procedure is concerned regarding the separation of L-Ala-D-boroPro and L-Ala-L-boroPro. As indicated above, only Pro-boroPro and Ala-boroPro are specifically disclosed in the specification, and thus results in a finding of non-enablement for 50% of the disclosed species.

In response to the foregoing, applicants have provided a declaration by a consultant to the

the C_{18} chromatographic method on page 21 of the specification is "unambiguous" in its description of how to separate L-Pro-D-boroPro from L-Pro-L-boroPro, while at the same time, the description of the silica gel chromatographic method on page 15 of the specification is "equivocal". In support of this position, declarant has pointed to the words "appears" and "probably" on page 15 of the specification. It is true that the words "appears" and "probably" are not present on page 21 of the specification. However, nowhere on page 21 of the specification is there any explanation of how the chirality of the carbon atom at issue (the carbon bearing boron) was determined, or what assumptions might have been made in assigning stereochemistry. Thus, with respect to the chirality of the carbon atom at issue, the description on page 21 is no more definitive than the description on page 15. The ability of the declarant to carry out a given purification and to correctly assign stereochemistry to chiral carbons is not directly at issue. Rather, the question is what the skilled chemist reading the specification would have concluded about what applicant has done. As it happens, the skilled chemist reading pages 15 and 21 would not have concluded that the C_{18} chromatographic method on page 21 would have succeeded, while at the same time, the silica gel chromatographic method on page 15 of the specification would have failed. One reasonable interpretation of the specification would have been that in separating stereoisomers of Pro-boroPro, one should use a reverse phase column.

interpret the specification as disclosing that "failure" will result if one were to attempt to purify Ala-boroPro on silica gel, the fact is that the claimed genus is of infinite size. For example, variable A' (claim 35) could represent a polymer of leucine. For this case, would a C₁₈ matrix necessarily provide a better separation than a silica matrix? The claimed genus of compounds runs the gamut from highly polar to very hydrophobic. Even if the skilled chemist were to conclude that people should selectively avoid procedures that are recommended in patent applications, the specification provides no guidance as to which procedures to avoid, or for which compounds.

Accordingly, enablement is lacking for attaining purified stereoisomers of the claimed compounds.

*

Claims 35, 36, 39-43, 46-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As indicated previously, each of claims 35, 39 and 42 recites that the stereochemical purity of the carbon atom bearing boron exceeds 96%, and that descriptive support for this is lacking. In response, applicants have pointed to the declaration filed 10/10/02, wherein

96-99% is intended. Whether that is true or not, the designation "99-6%" is even more consistent with the interpretation of 99.6%. Declarant has also argued that one can gain insight into applicants intentions by considering Gutheil (*Biochem* **32**, 8723, 1993). On page 8727 of that reference a procedure similar to that on page 21 of the application is described. It is stated in the reference that the purity of the greater than 98% was obtained. Declarant has argued that a purity in the range of 98-100% is consistent with a range of 96-99%. Again, however, a purity in the range of 98-100% is even more consistent with the interpretation of the designation "99-6%" meaning 99.6%.

Moreover, as indicated previously, in normal English usage, the lower number is presented first, i.e., 96 - 99%, rather than 99-96%. Accordingly, support is lacking both for the number 96 and for the number 99.

The rejection is maintained

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Claims 35, 36, 39-43, 46-51 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the claims, the abbreviation "DP-IV" may be used, if accompanied by the full name of the term that this abbreviation represents

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 35, 36, 39, 41, 42, 46, 47-49 are rejected under 35 U.S.C. §103 as being unpatentable over Bachovchin (*J. Biol. Chem.* **265**, 3738, 1990).

As indicated previously, Bachovchin teaches (page 3743, col 1, paragraph 3) acquisition of the requisite isomer, but that the purity was only 95%. If the requisite isomer can be obtained with 95% purity after only one pass through a column, an organic chemist of ordinary skill would have expected that a purity of at least 96% could be obtained after two passes. In response, applicants have pointed to the declaration (paper No. 58, filed 10/10/02), in which it is stated (paragraph 10) that the skilled chemist would have been

that of treatment of human disease, and the skilled chemist would have been motivated to use the D-isomer because of its greater *in vivo* lifetime. First, the compounds are also useful for *in vitro* testing (enablement for treatment of diseases is lacking). Second, more often than not, replacing L-isomers with D-isomers results in loss of activity when the compound at issue is a peptide inhibitor of a protease. This is especially true when replacing all of the L-amino acids with D-amino acids. In the instant case, however, the stereochemistry of only one chiral center is specified. There is no limit to the number of chiral carbons that may be present. For example, in claim 35, if A' represents a decapeptide, more than 2,000 stereoisomers could be present. The 10 chiral centers of A' would likely have a far greater effect (collectively) on inhibitory activity than the one chiral center which is principally at issue.

A second point made in the declaration filed 10/10/02 is to refer to the declaration filed 4/6/99 (paper No. 29). There is an argument to be made that if an applicant can provide evidence that the conclusions present in a given publication were erroneous, then that evidence can be effective to undermine the strength of a §103 rejection. However, in the instant case, any such undermining of the conclusions applies equally to the instant specification. The principle question is, to what extent is the claimed genus non-enabled? If agreement on this question can be reached, it might become appropriate at that point to

Serial No. 08/950,542
Art Unit 1653

- 9 -

At the present time, however, the rejection is maintained.

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Reference "DD 270382" was stricken from the IDS because it was not received.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.


DAVID LUKTON
PATENT EXAMINER
GROUP 1800